Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-131 are pending in this application and are rejected on various grounds. Claims 119-123 and 128 have been canceled without prejudice or disclaimer. Claim 124 has been amended with a functional recitation and Claim 130 has been amended for proper claim dependency. The rejections to the presently pending claims are respectfully traversed.

Specification

The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

In addition, amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Regarding the comment that pages 303-306 of the specification are missing, Applicants enclose a copy of the stamped return postcard received from the USPTO. This is *prima facie* evidence that all pages, including pages 303-306, were present at the time of filing of this application. For the Examiner's reference and convenience, Applicants have attached copies of pages 303-306 with this response.

Accordingly, Applicants believe that all objections to the specification has been overcome.

Claim Rejections – 35 USC § 101

Claims 119-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

The Examiner asserts that she is unable to find either in the specification or in the art, an explanation of how Ct values are calculated, nor what the significance of such are and concludes that "given the paucity of information, the data do not support the implicit conclusion that PRO341 shows a positive correlation with lung cancer". Further, the Examiner also alleges that since the data are not corrected for aneuploidy, and because it does not necessarily follow that an

increase in gene copy number results in increased gene expression, the data does not support that PRO341 or its antibody can be used as a cancer diagnostic. The Examiner specifically noted that "the utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey to the encoded protein or antibody that binds it" and therefore concludes that no asserted utility is specific for PRO341 protein.

Without admitting to the propriety of present rejections and solely in the interest of expediting prosecution in this case, claims 119-123 and 128 have been canceled and thus, rejections to these claims are obviated. Applicants respectfully disagree with and traverse the rejection of the remaining claims.

Claims 119-123 have been amended for clarity to recite "wherein the nucleic acid encoding said polypeptide is amplified in lung tumors". Applicants rely on the gene amplification assay for patentable utility which was first disclosed in U.S. Provisional Application 60/092182, filed July 9, 1998, priority to which has been claimed in this application. Hence, the effective filing date of the present application is **July 9, 1998.**

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 170 of the present application, where the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9A. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9A says that PRO341 showed approximately 1.12-1.33 ΔCt units which corresponds to $2^{1.12}$-$2^{1.33}$- fold amplification or **2.173 fold to 2.514-fold** amplification in lung tumors. This disclosure in the specification should address the Examiner's concerns regarding calculation of Ct values.

Further, to address the Examiner's issues concerning the TaqMan™ assay, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the

Examiner's attention to page 3 of the declaration which clearly states that:

> "It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy" (Emphasis added).

The Declaration also confirms that based upon the gene amplification results set forth in Table 9A, one of ordinary skill would find it credible that the PRO341 nucleic acid is a diagnostic marker of human lung cancer.

Regarding the Examiner's rejection based on a lack of explanation for aneuploidy, Applicants have enclosed a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, gene amplification of the PRO341 gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic for detection of lung cancer.

Regarding the Examiner's point that "no asserted utility is specific for PRO341 protein," Applicants submit, as discussed below, that the Examiner has not been established a *prima facie* case for lack of utility of the PRO341 polypeptide and also discuss the utility of the PRO341 polypeptide.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* According to the quoted statement, "WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient". From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation.

Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. Applicants once again rely on the Dr. Avi Ashkenazi's declaration which explains that,

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product".

Thus, Applicants have demonstrated utility for the PRO341 polypeptide. Hence, these data clearly support a role of PRO341 as a lung tumor marker. Accordingly, the present 35 U.S.C. §101 utility rejections should be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

Claims 119-131 are rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention". Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph because, according to Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing".

Further, the Examiner alleges that the specification does not enable the claimed variants of SEQ ID NO: 20 since Applicants provide little or no guidance beyond mere presentation of sequence regarding the positions which tolerate change and the nature and extent of changes that could be made in these positions; hence there was allegedly lack of adequate guidance to produce the claimed variants and hence one skilled in the art would not know how to make the claimed invention.

The Examiner additionally notes that Claims 119-124 and 129-131 encompass polypeptides that are structurally defined by reference to a biological deposit, ATCC accession number 209792 and points out that they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public.

In view of cancellation of claims 119-123 and 128, rejections to these claims are obviated. Applicants respectfully disagree with and traverse the rejection of the remaining claims.

In response to the previous rejection under 35 U.S.C. 101, Applicants have shown that PRO341 have utility since expression information regarding PRO341 provides significant information for cancer diagnosis and treatment. Hence, the rejection on the ground that the use of the claimed invention is not enabled should be withdrawn.

Further, Applicants submit that undue experimentation is not required of the skilled artisan to make and use the claimed invention recited in presently amended claims and hence, this rejection should be withdrawn.

Regarding the rejection based on the 'biological deposit,' amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." Thus, this rejection is obviated.

Regarding the rejection to the claimed genus for alleged lack of adequate written description, in view of the present claim cancellations and amendments, Applicants submit that the skilled artisan would reasonably accept that Applicants had possession of the claimed subject matter at the time of filing.

Hence, Applicants request that the present rejection to the present claims be reconsidered and withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-124 and 129-131 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleges that the protein identified as PRO341 has several transmembrane domains while the claims recite "the extracellular domain." The Examiner alleges that if there are several transmembrane domains there must be several extracellular domains, and it is unclear which extracellular domain is intended.

Initially, in view of cancellation of claims 119-123 and 128, rejections to these claims are obviated. Further, Applicants point out that it is well understood in the art that some proteins (for example, receptor proteins) have multi-pass transmembrane domains (that is, the polypeptide traverses the membrane, in this case, seven times) and still possess only one extracellular domain. Applicants attach an excerpt from the book "Molecular Biology of the Cell" 3rd ed. by Alberts, Bruce et al., Garland Publishing; c1994 for the Examiner's reference (see paragraph 3 and 4 of second attached page). Therefore, the "extracellular" domain recited in part (c) of the claims are clearly understood by people in the relevant art.

Further, part (d) of the claim has been deleted for clarity. Accordingly, Applicants submit that the phrase "the extracellular domain" is definite and respectfully request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 24, 2003

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